Antiplatelet therapy in myocardial infarction and coronary stent thrombosis

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Marked reduction of early stent thrombosis with pre-hospital initiation of high dose Tirofiban in ST-segment elevation myocardial infarction

An analysis of the On-TIME 2 trial

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SUMMARY

Background: No randomized comparisons are yet available evaluating the effect of pre-hospital high dose tirofiban on the incidence of early stent thrombosis after primary percutaneous coronary intervention (PCI).

Objectives: The aim of this analysis was to evaluate whether routine pre-hospital administration of high dose tirofiban in ST-segment elevation myocardial infarction (STEMI) decreases the incidence of early stent thrombosis after primary PCI.

Patients/Methods: The Ongoing Tirofiban in Myocardial Evaluation 2 trial was a prospective multicenter study of consecutive STEMI patients referred for primary PCI in which patients were randomized to pre-hospital high dose tirofiban or none. We examined the incidence of Academic Research Consortium definite and probable early stent thrombosis and determined predictors and outcome of early stent thrombosis.

Results: Primary PCI was performed in 1203 out of 1398 patients (86.1%). In 1073 patients (89.2%) a coronary stent was placed. Early stent thrombosis occurred in 39 patients (3.6%). Pre-hospital initiation of high dose tirofiban significantly reduced early stent thrombosis (2.1% vs. 5.2%, p=0.006) and was associated with a lower incidence of urgent repeat PCI (1.9% vs. 5.2%, p=0.005). Early stent thrombosis, as well as pre-hospital initiation of high dose tirofiban were independently associated with 30-day mortality

Conclusions: Pre-hospital initiation of high dose tirofiban reduces the 30-day incidence of stent thrombosis in STEMI patients treated with primary PCI and stenting. Early stent thrombosis and pre-hospital initiation of high dose tirofiban were independent predictors of 30-day mortality.

INTRODUCTION

As compared with thrombolytic therapy, primary percutaneous coronary intervention (PCI) for the treatment of acute ST-segment elevation myocardial infarction (STEMI) has reduced the rates of reinfarction and mortality [1,2]. The additional use of coronary stents has further reduced the rates of target-vessel revascularization (TVR) [3]. Despite these major improvements, the incidence of stent thrombosis (ST) is currently reported in one to five percent of real-world STEMI patients [4-6] Patients with a large thrombus burden are especially at risk of ST [7]. Many reports have emphasized the devastating effects of late or very late ST. However, few studies on the clinical consequences of early ST in patients with STEMI have been conducted [8-11]. Recently, it was postulated that in-hospital ST has relatively good outcomes [12]. The Ongoing Tirofiban in Myocardial Evaluation (On-TIME) 2 trial evaluated pre-hospital initiation of high-dose tirofiban (HDT) on top of dual anti-platelet therapy in STEMI patients [13].
In this post-hoc analysis of the On-TIME 2 trial, we assessed whether early pre-hospital initiation of HDT reduced stent related thrombotic complications and the effect of early ST on clinical outcomes.

METHODS

Patient population
The On-TIME 2 trial enrolled consecutive patients with STEMI who were candidates for primary PCI. In the run-in phase of the On-TIME 2 trial, two intervention centers in the Netherlands enrolled 414 patients in the ambulance to HDT or no HDT in an open-label randomized fashion. This open-label randomized phase was followed by a double-blind, placebo controlled phase which enrolled 984 patients in an international multicenter study [13]. Identical inclusion and exclusion criteria and concomitant treatment regimens were used in both phases from the On-TIME 2 trial. Patients were randomly assigned to pre-hospital initiation of HDT (tirofiban (25 μg/kg bolus and 0.15 μg/kg/min maintenance infusion) for 18 h) or no HDT in the ambulance in addition to 500 mg of aspirin (Aspegic®), 5000 IU unfractionated heparin administered intravenously, and a 600 mg loading dose of clopidogrel. For this post-hoc analysis data from the open-label randomized phase (414 patients) and the double-blinded randomized phase (984 patients) were combined (Figure 1). The study inclusion criteria for patients were age 21-85 years, symptoms of STEMI more than 30 minutes but less then 24 hours, and ST-segment elevation > 1 mV in 2 adjacent electrocardiogram (ECG) leads. Full exclusion criteria have been published previously [14]. Key exclusion criteria included known

severe renal dysfunction, therapy resistant cardiogenic shock, or increased risk for bleeding. Before primary PCI additional unfractionated heparin was administered only in cases where the activated clotting time was below 200 seconds. Informed consent was obtained in the ambulance or referring hospital. The study protocol of the On-TIME 2 trial for the open-label phase and the double-blinded phase was approved by all local ethical committees involved.

Clinical definitions and follow-up

Patients were included in the present analysis if they received at least one coronary stent at the time of primary PCI. ST was assessed according to the Academic Research Consortium (ARC) designations of definite and probable ST [15]. In brief, definite ST was defined as angiographic or pathological confirmation of ST and at least one of the following criteria within a 48-hour time window: clinical signs of ischemia, new ischemic ECG changes that suggested acute ischemia and typical rise and fall in cardiac biomarkers. Probable ST was defined as any unexplained death within the first 30 days after the index PCI. ST occurrences 0 to 24 hours after stent implantation were classified as acute and those occurring between 24 hours to 30 days after stent implantation were classified as subacute. Acute and subacute ST occurrences were then grouped together and defined as early ST (0 to 30 days). Detailed data on patient characteristics, angiographic and procedural characteristics of the index primary PCI were collected.

Detailed information on major adverse cardiac events such as death, recurrent myocardial infarction (MI), urgent TVR and TIMI major bleeding was collected through outpatient clinic visits, telephone interviews, hospital records, attending physicians or interviews with relatives. A blinded, independent clinical endpoint committee adjudicated all clinical endpoints apart from death. Recurrent-MI within 30 days after completion of the primary PCI was defined as a new increase of CK-MB > 3 times the upper limit of normal, whether or not it was accompanied by chest pain and/or ECG changes, and present in two separate blood samples. Early recurrent infarction according to the On-TIME 2 study protocol was defined as an increase in CK-MB of at least 50% of the upper limit of normal from a prior peak level to a valley followed by a new increase with a value above the sum of the preceding valley and three times the upper limit of normal. Urgent TVR was defined as any ischemia-driven revascularization performed in the same vessel as the index primary PCI with PCI or coronary artery bypass grafting (CABG). In case of urgent TVR, coronary angiograms of both the index procedure and the urgent TVR were reviewed by two experienced interventional cardiologists to diagnose ST. Bleeding was defined according to the Thrombolysis in Myocardial Infarction (TIMI) major or minor criteria. Detailed data on timing and cause of bleeding were also obtained.

Statistical analyses

Univariate analyses of predictors of the occurrence of ST were conducted with the chi-square test or Fisher's exact test for categorical variables, the chi-square for trend for ordinal variables, and the Mann-Whitney U test for continuous variables. Multivariate analyses of predictors of ST were done using logistic regression models. Logistic regression was also used to identify the multivariate predictors of mortality. Statistical analyses for predictors of ST and 30 day mortality were performed on the combined data from the On-TIME 2 trial double-blind and open-label studies. Baseline characteristics and outcome of the open-label phase and double-blinded phase were analyzed for similarity before combining the data. Survival estimates regarding stent thrombosis were calculated and compared using log-rank tests (time-to-event analysis). Kaplan-Meier curves were generated for visual analysis of survival. All p-values were two-sided with significance level $p < 0.05$. Statistical analyses were performed with SPSS for Windows (Rel. 15.0.1.1. 2007. Chicago: SPSS Inc.)

RESULTS

A total of 1203 out of 1,398 patients (86.1%) enrolled underwent primary angioplasty. In 1,073 patients (89.2%) a coronary stent was placed at the time of primary angioplasty and these patients form the basis of this report. Of these, 536 were randomized to pre-hospital HDT initiation and 537 were randomized to no HDT (Figure 1). Baseline clinical, angiographic, procedural, and outcome data according to randomization are shown in Table 1. After primary PCI, early (0-30 days) ST occurred in 39 patients (3.6%). According to the ARC designations ST was labeled definite in 37 cases and probable in 2 cases. ARC definite ST was confirmed in 36 cases after reviewing the angiograms of the urgent repeat PCI and in one case after postmortem pathological examination. ARC probable ST was suspected in two patients presented with chest pain and ST-segment elevation on the ECG obtained in the ambulance within 30 days after the index procedure. Both patients however were resuscitated unsuccessfully before angiography was possible and postmortem examination was refused in both cases. The reduced incidence of ST was associated with a significantly lower need for urgent TVR in patients randomized to HDT (5.4% vs. 2.5%, p=0.02) due to a reduced incidence of urgent repeat PCI (5.2% vs. 1.9%, p=0.005). Mortality at 30-days was also significantly lower in patients randomized to HDT (3.1% vs. 1.0%, p=0.02). In patients who suffered from ST 30-day mortality was significantly higher as compared to those who did not experience ST (10.3% vs.1.7%), p = 0.006). Independent predictors for thirty day mortality were Killip class II or higher at presentation, early ST, TIMI major bleeding, time from symptom onset to angioplasty > 4 hours, increasing age and no pre-hospital initiation of HDT (Table 2).

Table 1 Baseline, angiographic and procedural characteristics and 30-day clinical outcome

	Placebo (n = 537)	Tirofiban (n = 536)	p
Baseline characteristics*			
Age (years)	61.8 (11.5)	61.4 (11.6)	0.51
Sex (male) (%)	407 (75.8%)	421 (78.5%)	0.28
Hypertension (yes) (%)	169 (31.5%)	177 (33.1%)	0.59
Diabetes (yes) (%)	47 (8.8%)	56 (10.5%)	0.35
Hyperlipidemia (yes) (%)	128 (23.9%)	133 (25.0%)	0.68
Current smoking (yes) (%)	272 (51.1%)	260 (49.1%)	0.52
Family history of cardiovascular disease (yes) (%)	214 (40.5%)	220 (41.8%)	0.67
Body mass index (kg m^{-2})	26.9 (3.8)	27.0 (3.6)	0.52
Prior myocardial infarction (yes) (%)	40 (7.4%)	35 (6.6%)	0.58
Prior percutaneous coronary intervention (yes) (%)	35 (6.5%)	38 (7.1%)	0.70
Prior coronary bypass surgery (yes) (%)	7 (1.3%)	7 (1.3%)	0.99
Prior stroke (yes) (%)	7 (1.3%)	5 (0.9%)	0.57
Renal failure† (yes) (%)	66 (13.3%)	76 (15.1%)	0.40
Killip class II or higher (yes) (%)	66 (12.5%)	53 (10.0%)	0.21
Time from onset of symptoms to angioplasty (min)	166 (128 -256)	165 (129 -236)	0.80
Time from onset of symptoms to diagnosis (min)	77 (46 -146)	75 (45 -139)	0.43
Time from start study medication to angiography (min)	55 (43 -70)	55 (43 -70)	0.94
Time from start study medication to angioplasty (min)	72 (59 -90)	74 (59 -91)	0.70
Angiographic characteristics			
Type A of B1 lesion‡ (yes) (%)	234(44.2%)	228 (43.4%)	0.79
Type B2 or C lesion‡ (yes) (%)	295 (55.8%)	297 (56.6%)	
Infarct related vessel			
Left anterior descending coronary artery (yes) (%)	218 (40.7%)	222 (41.4%)	0.82
Left circumflex artery (yes) (%)	59 (11.0%)	70 (13.1%)	0.31
Right coronary artery (yes) (%)	254 (47.5%)	241 (45.0%)	0.41
Saphenous- vein graft (yes) (%)	3 (0.6%)	2 (0.4%)	0.69
Left main coronary artery (yes) (%)	1 (0.2%)	1 (0.2%)	> 0.99
Procedural characteristics			
Thrombus aspiration (yes) (%)	224 (60.2%)	216 (55.7%)	0.20
Balloon predilation (yes) (%)	332 (61.8%)	332 (61.9%)	0.97
Number of stents per patient (n)	1.3 (0.6)	1.4 (0.7)	0.48
Number of patients with drug eluting stents (yes) (%)	125 (23.3%)	142 (26.5%)	0.22
Number of patients with bare metal stents (yes) (%)	407 (75.8%)	383 (71.6%)	0.12
Number of patients with mixed stents (yes) (%)	5 (0.9%)	10 (1.9%)	0.19
Stent length (mm)	23.4 (10.3)	24.3 (13.2)	0.84
Stent diameter (mm)	3.3 (0.5)	3.3 (0.4)	0.31
Coronary flow infarct related artery after angioplasty			
TIMI 0-1 flow (yes) (%)	8 (1.5%)	7 (1.3%)	0.81
TIMI 2-3 flow (yes) (%)	522 (98.5%)	519 (98.7%)	

Clinical outcome at 30-days*			
Early (0-30 days) stent thrombosis	28 (5.2%)	11 (2.1%)	0.006
Acute (0-24 hours) stent thrombosis	16 (3.0%)	1 (0.2%)	< 0.001
Subacute (24 hours to 30 days) stent thrombosis	12 (2.2%)	10 (1.9%)	0.67
Urgent target vessel revascularization (yes) (%)	28 (5.4%)	13 (2.5%)	0.02
Urgent PCI (yes) (%)	27 (5.2%)	10 (1.9%)	0.005
Urgent CABG (yes) (%)	1 (0.2%)	3 (0.6%)	0.37
Death	16 (3.1%)	5 (1.0%)	0.02
Recurrent MI	14 (2.7%)	9 (1.7%)	0.30
Death, recurrent MI or urgent TVR (yes) (%)	43 (8.2%)	19 (3.7%)	0.002
TIMI major bleeding (yes) (%)	8 (1.5%)	8 (1.5%)	0.99

TIMI, Thrombolysis in Myocardial Infarction trial; BMI, body mass index; GFR, glomular filtration rate; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; MI, myocardial infarction; TVR, target vessel revascularization. Values are mean (standard deviation), median (interquartile range) or number (percentage of total number).
*** Percentages exclude patients with missing data. † Glomular filtration rate lower than 60 mL min $^{-1}$. ‡ Based on American College of Cardiology/American Heart Association classification.**

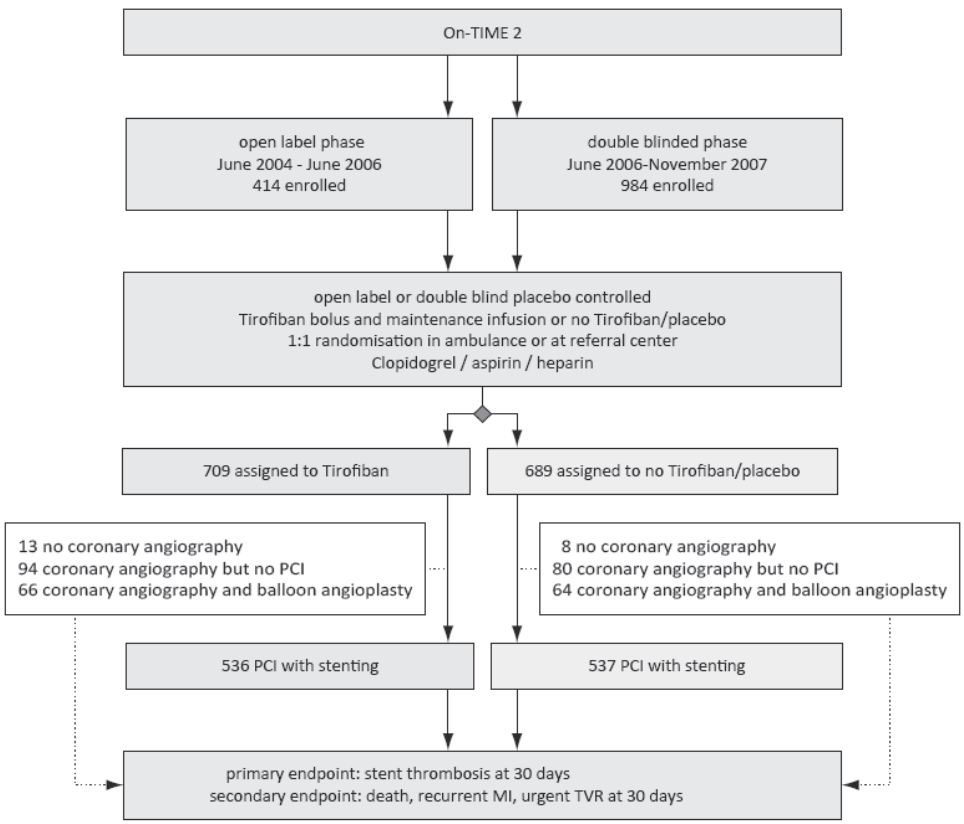

Figure 1 Study profile PCI, percutaneous coronary intervention; MI, myocardial infarction; TVR, target vessel revascularization; Green bar means assigned to Tirofiban; Red bar means assigned to no Tirofiban.

Table 2 Independent predictors of 30-day mortality

	Odds Ratio (95% Confidence Interval)	p
Killip class II or higher	9.0 (2.5-32.4)	0.001
Stent thrombosis	8.9 (2.1-37.1)	0.003
Age per 10 years increase	3.3 (1.5-7.4)	0.004
TIMI major bleeding	16.0 (2.4-109.3)	0.005
Randomization to no HDT/placebo	7.2 (1.4-36.4)	0.02
Time from onset of symptoms to angioplasty longer than 4 hours	3.6 (1.1-11.7)	0.04
Renal failure*	4.1 (0.97-17.5)	0.054
Weight per 10 kg increase	1.4 (0.9-2.2)	0.10
Infarct-related vessel is the LAD	2.4 (0.7-7.9)	0.15
Diabetes	2.2 (0.5-9.4)	0.30

TIMI, thrombolysis in myocardial Infarction trial; HDT, high dose tirofiban; LAD, left anterior descending coronary artery. *Glomular filtration rate lower than 60 mL min $^{-1}$)

Timing and predictors of early stent thrombosis

The incidence of ST in the open-label phase and the double- blind phase separately is shown in Figure 2. Acute ST (0-24 hours) occurred less frequently in patients randomized to HDT in the open label phase (0.0% (no case) vs. 3.4% (5 cases), p=0.024) and the double blind phase (0.3% (one case) vs. 2.8% (11 cases), p = 0.005) The incidence of subacute ST (24 hours to thirty days) was not significantly lower in patients randomized to HDT in the open label phase (0.6% (one case) vs. 2.7% (4 cases), p = 0.195) as well in the double blind phase (2.4% (9 cases) vs. 2.1% (8 cases), p = 0.739).

When the data of the open label and double blind phase were combined, the incidence of early (0-30 days) ST was 5.2% (28 cases) in the no HDT group and 2.1% (11 cases) in the HDT group (p = 0.006) (Figure 3). Acute (0-24 hours) ST occurred significantly less frequently in the HDT group as compared to the no HDT group (0.2% (one case) vs. 3.0% (16 cases), p < 0.001). The incidence of subacute (24 hours to thirty days) ST was similar in both groups (1.9% (10 cases) in the HDT group, 2.2% (12 cases) in the no HDT group, p = 0.67).

Independent predictors of ST were no HDT pretreatment (Odds Ratio (OR), 2.7; 95% Confidence Interval (CI), 1.3- 5.7;p = 0.007), smaller stent diameter per mm decrease (OR, 2.5; 95% CI, 1.1- 5.9, p = 0.04), and TIMI major bleeding (OR,9.0; 95% CI, 2.6- 31.6; p = 0.001) after adjustment for each of the other variables and previous AMI, previous PCI, previous stroke, Killip class II or higher and total stent length.

In four cases ST was associated with TIMI major bleeding. The first patient developed tamponade due to coronary artery perforation at the time of primary PCI treated with repeated balloon inflations, pericardiocentesis and Packed Cells. ST occurred six days

later. The second patient had a gastrointestinal bleed several hours after primary PCI managed endoscopic and with Packed Cells. ST occurred several hours later. The third and fourth patient developed groin bleeds day three and four after primary PCI, respectively. The bleeds were treated with compression therapy. ST occurred several hours later on the same day of the bleed in one patient and in the other five days later. Oral anti-platelet therapy (aspirin and clopidogrel) was not interrupted upon bleeding diagnosis in all four cases.

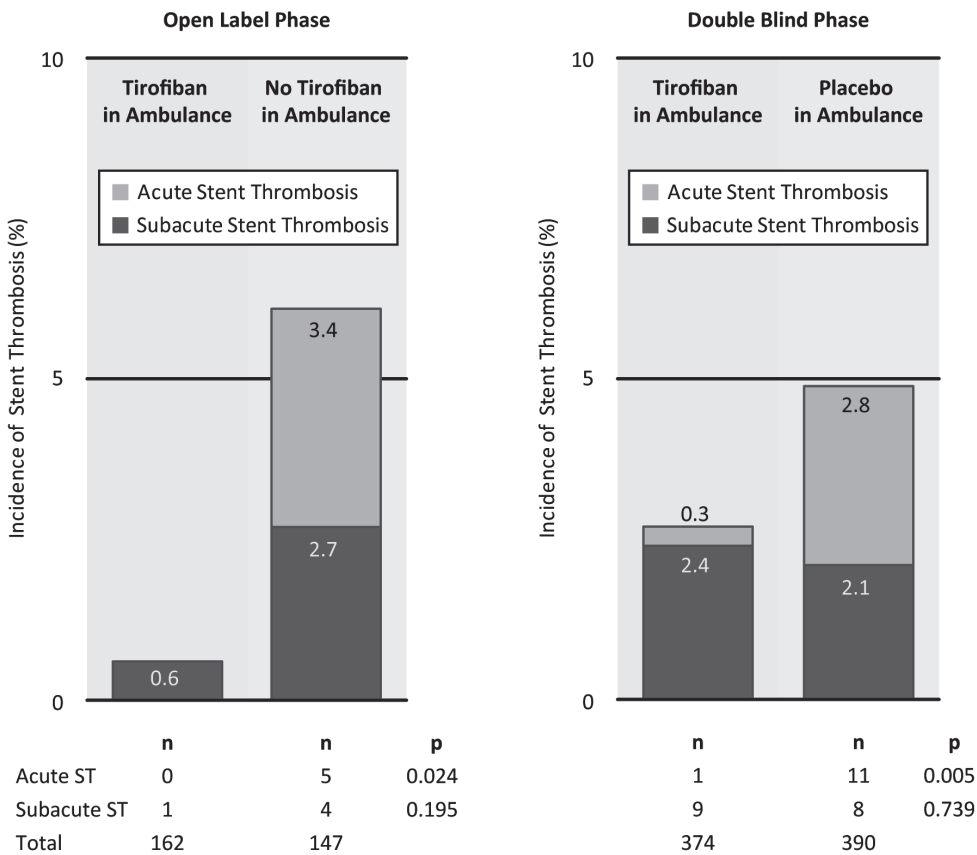

Figure 2 Thirty day incidence of stent thrombosis according to study phase ST, stent thrombosis.

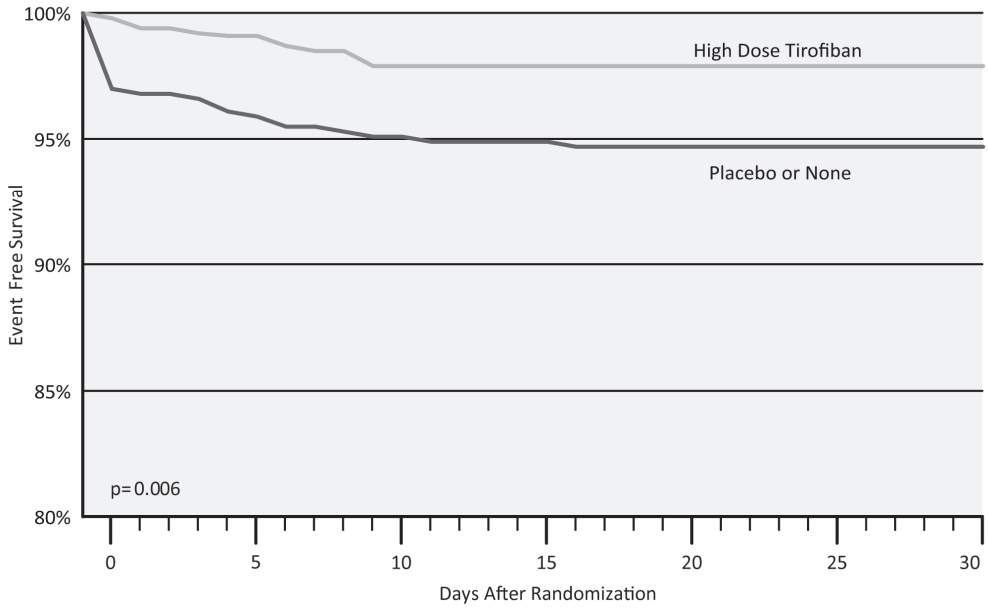

Figure 3 Thirty day event free survival from stent thrombosis

DISCUSSION

In the present study pre-hospital initiation of HDT in addition to aspirin, heparin and high dose clopidogrel reduced the incidence of early ST in STEMI patients undergoing primary PCI with stenting. Additionally, ST was shown to be an independent and strong predictor of mortality. A 3.1% absolute reduction in the incidence of early ST was observed in the HDT pre-treated group, a decrease mainly attributable to a reduction in acute ST. A likely explanation for this reduced incidence might be a higher procedural success with HDT pre-treatment as well as adequate thrombotic protection in patients with a suboptimal primary PCI result.

The reported incidence of early ST is relatively high in the On-TIME 2 trial. Nonetheless, the incidence seen in the present study is similar to the incidence of ST reported by the recently published MULTISTRATEGY study [5]. In a real-world STEMI population, the reported incidence of early ST was as high as 4% [4,6]. A plausible explanation for this finding is the heightened levels of platelet activation, large thrombus burden, and troubled stent sizing due to vasoconstriction of the target vessel in patients with STEMI. The On-TIME 2 study protocol included the administration of 600 mg clopidogrel in the ambulance. Platelet activation in the setting of STEMI is substantially increased and

the level of achieved inhibition of platelet aggregation from a high clopidogrel loading dose in the short time interval between loading dose and primary PCI (+/- 70 min) in the present study is probably insufficient to provide an optimal PCI result [16]. This is in line with a previous study which demonstrated a restricted effect of a 600 mg loading dose of clopidogrel in STEMI patients [17]. A significantly reduced gastrointestinal absorption of clopidogrel in STEMI patients was found, resulting in a significantly lower and delayed magnitude of platelet inhibition as compared to healthy volunteers [17]. With these data in addition to the findings of the present analysis one might conclude that a single high loading dose of clopidogrel in the setting of STEMI is not sufficient to achieve optimal inhibition of platelet activation within the first 24 hours and therefore is not the optimal treatment to prevent acute stent thrombosis.

The association of early ST with small stent diameter is not unexpected and is in agreement with previous reports on this issue [6-10]. A somewhat surprising observation in the present study was the relationship between TIMI major bleeding and the occurrence of ST. Importantly, in all cases bleeding preceded the onset of ST and none of these patients had discontinued anti-platelet therapy (aspirin-clopidogrel). This finding corresponds with findings from the ACUITY trial, which reported an increased incidence of ST in patients with TIMI major bleeding [18]. From this viewpoint it is important to highlight that the pre-treatment with HDT in the On-TIME 2 trial was not associated with an increased risk of TIMI major bleeding [13]. This is in contrast to the TRITON-TIMI 38 study which demonstrated that prasugrel, as compared to clopidogrel, significantly reduced ST after PCI in acute coronary syndromes, however at the cost of a significant increase in TIMI major bleeding [19].

We found a clear relationship between early ST and 30-day mortality. Previous reports have demonstrated a strong association between ST and mortality, especially in patients with late ST [7-11]. Our study adds to this body of evidence and clearly shows that also acute and subacute ST is associated with a poor outcome. Therefore, all possible efforts should be directed to preventing this severe complication of PCI. Routine administration of HDT to STEMI patients who are candidates for primary PCI in the ambulance en route to the referring hospital is a step in the right direction to achieving this goal. The favorable effects of reduced ST in this study in addition to the demonstrated improved ST-segment resolution in the main-study of the On-TIME 2 trial further support routinely pre-hospital administration of HDT in STEMI patients referred for primary PCI [13]. This combined improvement of ST resolution after PCI and the reduction of early stent thrombosis is probably the mechanism of the reduced 30 day mortality with early initiation of HDT in the ambulance, as found in this analysis.

Recently, the HORIZONS trial showed that bivalirudin monotherapy is associated with a significantly higher incidence of acute ST as compared to routine use of GP 2b3a

blockers [12]. Although this did not affect overall clinical outcome in this trial, the present study showed ST to be an important predictor of death. One might argue the clinical impact of acute ST, which often occurs when the patient is still hospitalized and is often treated with urgent repeat PCI. A recent study, however, showed that angioplasty for STEMI due to ST often results in unsuccessful myocardial reperfusion [9].

In the present study, TIMI major bleeding was also strongly associated with 30-day mortality. This finding is in line with previous reports demonstrating the adverse effect of periprocedural bleeding on short-term and long-term mortality [20]. In our report, early ST was a strong independent predictor of 30-day mortality besides TIMI major bleeding. This finding again emphasizes the devastating consequences of early ST.

There are several aspects of this analysis that merit careful consideration. First, data from two phases of the On-TIME 2 trial with different design (open-label versus double-blind) were combined. However, both study phases had identical in- and exclusion criteria and baseline characteristics and outcome of patients included in both study phases were similar. Second, the definition of early recurrent-MI used in the On-TIME 2 protocol was based upon laboratory markers. In all cases of acute ST, clinical evidence of recurrent myocardial ischemia with renewed chest pain and a new increase in ST-segment elevation was present. However, in many cases of acute ST, the strict study criteria for early recurrent-MI based upon laboratory markers were not met. In conclusion, pre-hospital initiation of high dose tirofiban in addition to aspirin, heparin and high dose clopidogrel reduced the 30-day incidence of stent thrombosis and mortality in STEMI patients treated with primary PCI. Early stent thrombosis and pre-hospital initiation of HDT were independent predictors of 30-day mortality.

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